TZU CHI MED J June 2009 Vol 21 No 2

available at http://ajws.elsevier.com/tcmj

Tzu Chi Medical Journal

Original Article

A Clinical Study of Prognosis and Glucocorticoid Pulse Treatment in Patients with Acute Paraquat Intoxication

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Article info

Article history:
Received: June 20, 2008
Revised: August 25, 2008
Accepted: October 27, 2008

Keywords:
Methylprednisolone pulse therapy
Paraquat
Prognosis
Severity index of paraquat poisoning

Abstract

Objective: Paraquat is a highly toxic herbicide that binds strongly to tissue and causes high mortality rates due to pesticide intoxication in Taiwan. In this study, we evaluated the usefulness of methylprednisolone pulse therapy and calculation of the severity index of paraquat poisoning (SIPP) to predict the prognosis in patients with oral paraquat intoxication.
Materials and Methods: Thirty-two patients with paraquat poisoning from January 2003 to April 2005 were enrolled into this study at a medical center in eastern Taiwan. All 32 patients had history of oral intake of paraquat and urine paraquat was positive at the emergency department. Time of oral intake of paraquat and serum paraquat levels were assayed at the emergency department for calculating SIPP (hour×mg/L) level. Sixteen patients with oral paraquat poisoning were treated with intravenous methylprednisolone 1 g/day and charcoal hemoperfusion for 3 days (MP group), and 16 patients with oral paraquat poisoning were treated with charcoal hemoperfusion only for 3 days (control group).
Results: The mortality rate of the patients with oral paraquat poisoning was high (87.5%). There were no statistically significant differences in death ($p=1.000$), age ($p=0.706$), sex ($p=0.069$), serum blood urea nitrogen ($p=0.104$), creatinine ($p=0.174$), aspartate aminotransferase ($p=0.083$), alanine aminotransferase ($p=0.365$), plasma level of paraquat ($p=0.880$) and SIPP level ($p=0.734$) between the MP group and control group. Young age ($p=0.030$), lower initial plasma paraquat level ($p=0.002$), lower serum creatinine ($p=0.009$), female sex ($p=0.033$), lower elapsed time from ingestion of paraquat to arrival at hospital ($p=0.035$) and SIPP level less than 10 ($p<0.001$) were associated with survival in patients with oral paraquat poisoning. Multivariate forward stepwise linear regression analysis of deaths showed that SIPP > 10 (hour×mg/L) ($p<0.001$) was an independent predictor of death in patients with oral paraquat poisoning and explained 77.1% of the variance ($R^2=0.771$).
Conclusion: Treatment with methylprednisolone pulse therapy did not show better results in patients with acute oral paraquat poisoning. SIPP was an independent predictor of death in patients with oral paraquat poisoning.
(*Tzu Chi Med J* 2009;21(2):156–160)

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1. Introduction

Paraquat is a contact herbicide that is used worldwide due to its rapid inactivation in the environment [1]. Intentional and accidental ingestion of commercial liquid formulations of paraquat has caused a large number of human fatalities in Taiwan [2]. Ingestion of a large amount of paraquat is considered to be fatal, resulting in death due to multiple organ failure and cardiogenic shock within 1–4 days [3]. There are three degrees of severity in paraquat poisoning [1]. Mild poisoning can cause oral irritation and gastric upset, and the prognosis is complete recovery. Moderate to severe poisoning leads to acute renal failure and, in severe cases, hepatitis followed by pulmonary fibrosis, and death after 2–3 weeks. Patients with acute fulminant paraquat poisoning die from multiple organ failure and cardiogenic shock within 7 days. Oxygen free radical generation and neutrophil-mediated inflammation are responsible for toxicity in humans by producing injury to intracellular membranes and organelles and eventually cell death [4]. Therapy has concentrated on reducing paraquat absorption from the gastrointestinal tract and increasing its elimination [3]. However, there is no clinical evidence that reducing absorption using Fuller's earth, activated charcoal, or increasing elimination by forced diuresis, hemodialysis, hemofiltration, hemoperfusion or continuous venovenous hemofiltration has increased survival in patients with paraquat poisoning [3,5]. Methylprednisolone has potent anti-inflammatory and immunosuppressive properties [6]. Single high dose dexamethasone treatment decreases the pathological scores and increases the survival rate after paraquat intoxication in rats [7]. Recently, researchers have reported methylprednisolone pulse therapy that can prevent the further damage of lung tissue during the subacute period of paraquat intoxication in humans [8,9]. The aim of this study was to investigate the efficacy of methylprednisolone pulse therapy in patients with acute paraquat poisoning. We used severity index of paraquat poisoning (SIPP) to predict the prognoses in patients with acute paraquat intoxication.

2. Materials and methods

2.1. Patients

Thirty-two patients with oral paraquat poisoning were enrolled in this study from January 2003 to April 2005 at a medical center in eastern Taiwan. All 32 patients had positive urine paraquat levels detected using sodium dithionite reaction in the emergency department (ED). The Protection of Human Subjects Institutional Review Board at Tzu Chi University and Hospital approved this study. Patients were excluded from this study if they had dermal exposure to paraquat; received intravascular injection of paraquat; did not have paraquat levels in their biological fluids; arrived in the ED >24 hours after ingestion of paraquat; ingested paraquat due to major systemic diseases including cancer, heart, lung, renal, and liver diseases; or did not give informed consent.

2.2. Study protocol

Patients were assigned to receive either methylprednisolone (MP) pulse therapy with charcoal hemoperfusion (MP group) or only charcoal hemoperfusion (control group). Patients in the MP group were treated with intravenous MP 1 g on the first day, charcoal hemoperfusion every 4 hours on the first day and 50 g oral activated charcoal every 6 hours for 3 days in the intensive care unit. Patients in the control group were treated with charcoal hemoperfusion every 4 hours on the first day and 50 g oral activated charcoal every 6 hours for 3 days in the intensive care unit.

2.3. Biochemical investigations

Urine and blood samples were taken on arrival at the ED and were used to detect urine paraquat levels using sodium dithionite reaction and plasma paraquat levels with the spectrophotometry method (Beckman DU-650, CA, USA). Serum levels of blood urea nitrogen (BUN), creatinine (Cr), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured using an autoanalyzer (Hitachi 747, Tokyo, Japan) in the ED. The elapsed time (hours) from ingestion of the paraquat to arrival and serum paraquat levels was assayed in the ED to calculate the SIPP. SIPP (hour×mg/L) means elapsed time (hour)×serum paraquat level in the ED (mg/L). We used SIPP=10 (hour×mg/L) to indicate the boundary for survival and death as reported by Yamamoto et al [10].

2.4. Statistical analysis

Data are expressed as case number and were analyzed using the χ^2 test. Other data are expressed as mean±standard deviation and compared using the nonparametric Mann-Whitney U test. A p value<0.05 was considered statistically significant. All statistically significant variables ($p<0.05$) were put into a multiple linear regression model as independent variables and mortality was used as a dependent variable. Data were analyzed using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) for Windows.

Table 1 — Characteristics of paraquat intoxication in the methylprednisolone (MP) and control groups*

	MP group (n=16)	Control group (n=16)	$p^{\dagger}$
Sex			0.069
Male	12 (75)	7 (43.8)	
Female	4 (25)	9 (56.3)	
Survival			1.000
No	14 (87.5)	14 (87.5)	
Yes	2 (12.5)	2 (12.5)	
SIPP (hr×mg/L)			0.625
≤10	2 (12.5)	3 (18.8)	
>10	14 (87.5)	13 (81.2)	

*Data are presented as n (%); $^{\dagger}\chi^2$ test. SIPP = severity index of paraquat poisoning.

Table 2 — Comparison of parameters between the methylprednisolone (MP) and control groups*

	MP group (n=16)	Control group (n=16)	$p^{\dagger}$
Age (yr)	43.5±4.2	44.2±15.6	0.706
Plasma paraquat level (mg/L)	47.8±97.3	17.5±20.5	0.880
BUN (mg/dL)	29.9±35.9	13.8±8.1	0.104
Creatinine (mg/dL)	3.5±2.9	2.8±2.8	0.174
AST (U/L)	163.6±263.3	43.5±28.4	0.083
ALT (U/L)	54.9±60.3	33.3±26.2	0.365
Survival time (hr)	40.4±25.1	63.5±95.9	0.927
Time to arrival (hr)	6.4±4.4	6.7±4.8	0.492
SIPP (hr×mg/L)	320.8±815.6	107.9±148.0	0.734

*Data are presented as mean±standard deviation; †nonparametric Mann-Whitney U test. BUN = blood urea nitrogen; AST = aspartate aminotransferase; ALT = alanine aminotransferase; SIPP = severity index of paraquat poisoning.

3. Results

The comparison of clinical and laboratory profiles between the MP group and the control group are shown in Tables 1 and 2. There were no significant differences in gender, survival, age, plasma paraquat level, serum BUN, Cr, AST, ALT, survival time, time to arrival or SIPP levels between the MP group and control group.

The mortality profiles of paraquat intoxication patients are shown in Table 3. The mortality rate of patients with oral paraquat poisoning was high (87.5%). Most patients with paraquat poisoning in our study were fulminant and died within 7 days after paraquat intoxication. Among the 32 patients in our study, 28 died and four survived. Young age (p=0.030), lower initial plasma paraquat level (p=0.002), lower serum Cr (p=0.009), female sex (p=0.033), lower elapsed time from ingestion of paraquat to arrival at hospital (p=0.035) and SIPP level less than 10 (p<0.001) were associated with survival. Although being female was statistically associated with survival, equal numbers of male and female patients died and the difference was very small. There were no statistically significant differences in survival between the MP group and the control group, plasma paraquat level, serum BUN, AST, ALT and time to arrival.

Table 3 — Survival profiles of patients with paraquat intoxication

Characteristic	Dead (n=28)	Alive (n=4)	p
Group*			1.000
MP	14	2	
Control	14	2	
Sex*			0.033‡
Male	13	0	
Female	13	4	
SIPP (hr × mg/L)*			<0.001‡
≤10	1	4	
>10	27	0	
Age (yr)†	45.79±14.56	30.25±6.24	0.030‡
Plasma paraquat level (mg/L)†	37.29±74.77	0.25±0.19	0.002‡
BUN (mg/dL)†	23.50±28.35	10.00±4.24	0.188
Creatinine (mg/dL)†	3.51±2.88	0.88±0.15	0.009‡
AST (U/L)†	98.11±194.96	141.50±211.74	0.732
ALT (U/L)†	36.79±37.01	95.00±81.03	0.110
Time to arrival (hr)†	7.04±4.57	3.00±1.41	0.035‡

*Data are presented as n and analyzed using χ^2 test; †data are presented as mean±standard deviation and analyzed using nonparametric Mann-Whitney U test; ‡p<0.05. MP = methylprednisolone; SIPP = severity index of paraquat poisoning; BUN = blood urea nitrogen; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Table 4 — Multivariate stepwise linear regression analysis of sex, severity index of paraquat poisoning (SIPP), age, plasma paraquat level, time to arrival and creatinine: correlation to survival in patients with paraquat intoxication

	β	R^2	p
SIPP>10 (hr×mg/L)	−0.823	0.771	<0.001*

*p<0.05 is considered statistically significant in multivariate stepwise linear regression analysis.

Multivariate forward stepwise linear regression analysis of the mortality rate showed that SIPP >10 was an independent predictor of death in patients with paraquat poisoning (R^2=0.771; p<0.001) (Table 4).

4. Discussion

Our study showed that treatment with methylprednisolone pulse therapy did not improve the survival rate in patients with paraquat poisoning. SIPP was an independent predictor of death in patients with oral paraquat poisoning.

Paraquat (1,1′-dimethyl-4,4′-bipyridyl) is a contact herbicide that is used worldwide [1]. The production

of free radicals by single electron reduction during photosynthesis is responsible for the herbicidal action of paraquat [11]. Oxygen free radicals are responsible for toxicity in humans by producing injury to intracellular membranes and organelles and eventually cell death [4]. The lung is the primary target organ because of the active, energy-dependent uptake of paraquat by alveolar epithelium via the polyamine uptake pathway [11,12]. Initially, there is alveolitis which then progresses to fibrosis and results in death from hypoxemia [11,12]. The estimated lethal dose in adults is about 3–6 g of paraquat ions [12]. Lin et al reported that severe inflammation plays a critical role in producing lethal hypoxemia in patients with paraquat poisoning and combined repeated methylprednisolone pulse therapy preceding continuous dexamethasone treatment can attenuate the severe inflammation from severe paraquat poisoning [9]. They also used 1 g cyclophosphamide per day for 2 days and 1 g methylprednisolone per day for 3 days to treat patients with moderate-to-severe paraquat poisoning (survival >7 days after paraquat poisoning patients), and their results demonstrated that pulse therapy with cyclophosphamide and methylprednisolone may be effective in treating patients with moderate to severe paraquat poisoning, but it was not effective in treating patients with fulminant paraquat poisoning [13]. In our study, there were no significant differences in the biochemical data and survival between the MP group and control group. The reason may be that in our study, most of the patients had fulminant paraquat poisoning and not moderate to severe paraquat poisoning. Further studies are needed to assess the benefits of methylprednisolone pulse therapy in patients with moderate-to-severe paraquat poisoning.

Proudfoot et al showed that survival was determined by two primary variables: time elapsed since ingestion and plasma paraquat levels [14]. Lee et al [15] and Hong et al [16] reported that initial parameters other than plasma paraquat concentration, including blood pH, $PaCO_2$, age, respiratory rate, hemoglobin, white blood cell count, BUN, amylase, and the number of failed organs, were associated with survival after paraquat poisoning. Sawada et al reported that such survival curves were of limited use in the quantitative evaluation of the severity of poisoning and developed SIPP [17]. Yamamoto et al reported that SIPP=10 (hour×mg/L) indicated the boundary for survival and death [10]. In our study, time elapsed since ingestion of paraquat, serum BUN, AST and ALT were not associated with death. SIPP level less than 10, young age, female sex, low initial plasma paraquat level, lower elapsed time from ingestion of the paraquat to arrival at hospital, and low serum Cr level were associated with survival in patients with paraquat poisoning. In our study, female patients with paraquat poisoning had lower initial plasma paraquat levels than male patients with paraquat poisoning (female, 17.03±17.52 mg/L; male, 39.49±90.04 mg/L). However, there were no significant differences in the initial plasma paraquat levels between the female and male patients (p=0.384). Moreover, multivariate forward stepwise linear regression analysis of the mortality rate showed that SIPP >10 was an independent predictor of death in patients with paraquat poisoning and explained 77.1% of the variance.

Our study has some limitations. First, the number of patients enrolled was small and more patients are needed for further analysis. Second, this study did not check the serum paraquat levels during or after treatment in the MP group and the control group. Further studies are needed to show the association of prognosis with serum paraquat levels at different days after treatment in the MP group and the control group.

In conclusion, treatment with methylprednisolone pulse therapy did not improve survival in patients with oral paraquat poisoning. SIPP was an independent predictor of death in patients with oral paraquat poisoning.

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